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(54) Title: NON GELATIN FILMS WITH IMPROVED BARRIER PROPERTIES

(57) Abstract: Non gelatin film materials, e.g. hydroxy propyl methyl cellulose comprise e.g. an additive or additives such as an organic acid, e.g. hydroxy carboxylic acid, which form a barrier composition. The resultant films are safe human consumption and find use as a wall material of an ingestible delivery capsule, e.g. containing a dose of a pharmaceutical preparation.

NON GEL[redacted]N FILMS WITH IMPROVED BARR[redacted] PROPERTIES

Field of the Invention

This invention relates to modified polymeric materials and more particularly films of the modified cellulose material hydroxy propyl methyl cellulose (HPMC), and uses of such film.

Background of invention

HPMC is a synthetic plastics material, which is a chemically modified form of the naturally occurring polymer, cellulose. Films, (or sheets or membranes) of HPMC are available commercially and have various uses, including proposals for use as wall materials for delivery capsules i.e. capsules designed to retain and protect their contents until an intended site of delivery or conditions of delivery are encountered, at which the contents of the capsule are released. HPMC is suitable for ingestion by humans, so delivery capsules with HPMC walls find the potential use as ingestible capsules, e.g. for the delivery of accurately metered doses of pharmaceutical preparations and dietary supplements, as a possible replacement for gelatin based capsules. See for example, WO 97/35537, WO00/27367 and WO01/03676. HPMC can be used to encapsulate substances, such as pharmaceuticals or food supplements like fish oils. It is known that certain pharmaceuticals and food supplements can be prone to attack by extended exposure to e.g. air, and It is preferable to encapsulate many unrefined vegetable oils and fish oils to prevent them from going rancid. However, even when these substances are encapsulated, .e.g. within HPMC film, they can still be prone to oxidation, e.g. by the film wall of the capsule allowing oxygen present in the air outside the capsule, to pass through into the inside of the capsule and coming into contact with the capsule's contents, and reacting in some way to spoil the contents.

HPMC has poor resistance to oxygen transmission relative to other hydrocolloid film forming materials, such as gelatin, alginates, pectins and some other natural polymers. To improve oxygen barrier properties of the HPMC film, the film can be coated with hydrocolloids, for example, alginates. However, the coating of these films does give rise to certain disadvantages, such as creating films with multiple layers of materials each layer perhaps possessing different physical/chemical properties and thus creating increased processing complexities and problems arising therefrom, resulting in an increase in time and costs for film production.

Glycols and acetins are already known as film additives for certain film materials, but untreated films and films treated with acetins and /or other additives can show very poor resistance to oxygen penetration. However, it has now been surprisingly

discovered that by incorporating various carboxylic acids, especially alpha hydroxy acids and beta hydroxy acids within HPMC film, it is possible to reduce the oxidation of vegetable and fish oils, and other oxidisable fill materials encapsulated in capsules made from this film.

It should be noted that this invention is not limited to simply HPMC film materials. HPC (hydroxy propyl cellulose), MHEC (methyl hydroxy ethyl cellulose), HEC (hydroxy ethyl cellulose), EHEC (ethyl hydroxy ethyl cellulose), EC (ethyl cellulose) and MC (methyl cellulose) are all materials which can be included.

Summary of the invention

In the widest scope the of the invention, further polymeric films are contemplated, within a group which can be defined as non-gelatin polymeric films.

In one aspect of the present invention provides hydroxypropyl methyl cellulose film, comprising hydroxypropyl methyl cellulose and an additive comprising an organic acid, or derivative or salt of such an acid.

Suitable organic acids are carboxylic acids, such as mono, di, tri, or tetra or other polyvalent carboxylic acids.

Carboxylic acids according to the present invention include the following:

C1-C6 saturated or unsaturated, straight or branched chain carboxylic acids, with 1,2,3 or 4 carboxyl groups
C1-C6 hydroxy acids with any combination of 1,2,3,4 hydroxyl/carboxyl groups, including alpha hydroxy acids (AHA's) and beta hydroxy acids (BHA's)
Cyclised acids and cyclised hydroxy acids

Specific examples of acids according to the present invention include the following:

carboxylic acids

Adipic acid
Fumaric acid
Maleic acid
Proprionic acid
Salicylic acid
Ethanoic acid
Propanoic acid
Butanoic acid

Pentanoic acid
Hexanoic acid

hydroxy acids

Alpha hydroxy butyric acid
Mandelic acid
Tartaric acid
Lactic acid
Citric acid
Malic acid
Glycolic acid
Hydroxy citric acid

cyclised acids and cyclised hydroxy acids

Gamma butyrolactone
Gamma valerolactone
Beta propriolactone

HPMC films can be treated with alpha and beta hydroxy acids and also other carboxylic acids derived from fruit acids to produce clear films which can then be used to produce capsules which can significantly reduce oxidation of certain substances encapsulated within same as compared with capsules made form HPMC treated with compounds such as glycerine, propylene glycol, poly ethylene glycol and acetins. This significant improvement in the reduction of oxidation is thought to be attributable to the acid additive incorporated within the film perhaps hindering oxygen transmission through the film.

These films can be improved or modified further to suit the application by coating these films with aqueous solutions containing the acids according to the present invention.

Therefore, in a first aspect of the invention, the one or more acids are incorporated within the film by admixing the acids within a film forming resin which is then formed into a film.

In a second aspect of the invention, aqueous solutions of the acids are applied to the surface of a preformed film.

In a third aspect of the present invention, aqueous solutions of one or more acids are applied to the surface of films which are then bonded together.

In a fourth aspect of the present invention, aqueous solutions of one or more acids are applied to the surface of one or more capsule(s) made from film according to the present invention.

Film Manufacture

HPMC is dissolved in water with an acid or acids according to the present invention e.g. citric acid, to make a solution of which the total solids being between 10-20% w/w. (During this procedure, optional ingredients such as dyestuffs, sweeteners and manufacturing aids can be added.) The resultant viscous solution is then de-aerated and extruded at a set thickness onto a moving (endless) steel belt of which, during the length of its travel is heated to 80-100 degrees centigrade. During this heating process, water is evaporated from the film, leaving a dry film of thickness between 20-150 microns. This film is then removed from the belt and is further processed for use, e.g. slitting to a final roll width, laminating the single ply film to yield a double ply film, or coating with an external coat to give a specific desired property. Alternatively, for smaller quantities of film, a viscous solution can be poured onto a flat sheet of glass, and allowed to settle to form a flat bed of viscous liquid which lies on top of the glass. This can then be introduced into an oven at the desired temperature, where it can be left to dry , to form a desired sheet of film.

Alternatively to the above, a film can be formed as above but without the inclusion of the one or more acids within the film as the film is formed. Once the film has been formed, an aqueous solution of the one or more acids is applied to the surface of the film.

Preparation of capsules

A film solution consisting of HPMC and acid according to the present invention (total solids 10%) is cast onto glass plates to a set thickness. The cast film is then placed in a warm oven (50-80 degrees centigrade) to form a rigid film , which is then removed from the glass plate and left to equilibrate at room temperature. The resulting film produced is then placed on a vacuum forming bed and thermoformed into cavities or half capsules. Each cavity is filled (overfull) with fish or vegetable oil and lidded with

an identical sheet of HPMC film. A heated tool is then used to seal the films together and to cut the resulting capsules free of excess unused film surrounding the cavities. The capsules formed are removed from the bed and packed and placed in storage.

Stability testing

The stability of fish and vegetable oils were evaluated in the capsules made in accordance with the present invention. The stability of the oil in the capsules was evaluated by analysing the peroxide value (P.V.) over time.

Using a standard pharmaceutical test, samples were prepared and stored in HDPE bottles at 30 degrees centigrade, 60% relative humidity. Periodically, the samples were removed and analysed according to method described in the European Phamacopea: Peroxide Values Ph.Eur. method 2.5.5.

The results were plotted graphically to show comparative changes in P.V. over time.

Control capsules were made from HPMC film incorporating acetins (mono and diacetin).

The results can be interpreted thus: The higher rate of peroxide generated in the oil, the less stable is the end product.
Therefore , the best performing films show lower peroxide values.

Formulations:

Graph/fig. 1 , 2 and 4

	%w/w
HPMC (Methocel E50 ex Dow)	77
Diacetin	23
HPMC	77
Lactic acid	23
HPMC	77
Lactic acid	11
Citric acid	12
HPMC	77
Citric acid (anhydrous)	20
Glycerin	3
HPMC	77
Citric acid (anhydrous)	23

Graph/fig 3

HPMC	77
Monoacetin	23
HPMC	77
Lactic acid	23
HPMC	77
Malic acid	23
HPMC	77
Citric acid	23

Interpretation

Figure 1 – graph 1 capsules containing evening primrose oil (EPO)

Demonstrates the superior performance of HPMC incorporating citric acid or citric acid/glycerin combinations within the capsule film, by revealing generally lower and slowly rising peroxide values over a 5 month period. A 1:1 lactic/citric combination in the film still demonstrates very good performance and films treated solely with lactic acid still show a marked improvement over the performance of film treated with diacetin (control), a known film additive.

Figure 2 – graph 2 capsules containing fish oil (Lipromega TG60)

General trends shown in graph 1 are also demonstrated here. A vast improvement in maintaining low P.V. is shown. demonstrated by the stark stablizing effect of citric acid.

Figure 3 – graph 3 capsules containing fish oil (Lipromega TG60).

In this test, capsules were exposed directly to the atmosphere (without any packaging around the capsules). HPMC films containing citric, malic and lactic acid (especially citric and malic acids) demonstrated superior performance with respect to peroxide values, over HPMC films containing monoacetin.

Figure 4 – graph 4 - Na Alginate coated HPMC film with various plasticisers encapsulating EPO.

Comparing this with graph 1, this shows additional stabilization of peroxide values, which can be maintained for a longer period of time, due to the sodium alginate coating on the HPMC film.

Claims

1. A non gelatin polymeric film, comprising a non gelatin polymer and a barrier composition comprising an organic acid or a salt of an organic acid.

2. A non gelatin film according to claim 1 wherein the film comprises one or more of HPMC, MHEC , HEC , EHEC , EC and/or MC.

3. A non gelatin polymeric film, comprising hydroxypropyl methyl cellulose and a barrier composition comprising an organic acid or a salt of an organic acid.

4. A hydroxypropyl methyl cellulose film, comprising hydroxypropyl methyl cellulose and a barrier composition comprising an organic acid or a salt of an organic acid.

5. A film according to claim 1, wherein the organic acid is a carboxylic acid.

6. A film according to claim 1 wherein, the organic acid comprises one or more of maleic acid, fumaric acid, adipic acid, citric acid, lactic acid.

7. A film according to claim 1 wherein the organic acid comprises citric acid.

8. A film according to claim 1 wherein the organic acid comprises malic acid.

9. A film according to claims 1-5 wherein the organic acid is present in the amount in the range 5 to 40% by weight of the total weight of the film.

10. A film according to claims 1-6 comprising about 23% by weight of organic acid and 77% by weight of HPMC.

11. A film according to any one of the preceding claims, wherein the film is foamed, expanded or gasified.

12. A film according to any one of the preceding claims wherein the film has a thickness of between 20 to 250 microns.

13. A film according to any one of the preceding claims, wherein the film is additionally treated with a solution comprising one or more acids as defined in any previous claim.

14. A 2-ply film made from the films according to any previous claim, wherein the 2 films are bonded to one another by a solution comprising one or more acids as defined in any previous claim and/or further treated with said acids.

15. A delivery capsule with an enclosing wall comprising a film of composition in accordance with any one of the preceding claims.

16. A method of producing HPMC film suitable for forming into a capsule, comprising treating the HPMC film with acids in any preceding claim, before and/or during when the film is formed into a capsule.

17. A delivery capsule, whose walls provide a continuous barrier for protecting and containing the capsule's contents, said barrier comprising:
    a) a non-gelatin polymeric film
    b) an organic acid

18. A delivery capsule as defined in claim 16, wherein the non-gelatin film comprises HPMC

19. A delivery capsule as defined in claim 16, wherein the organic acid is a carboxylic acid

20. A method of treating a non gelatin polymeric film comprising:
    a) making a solution of one or more organic acids
    b) applying said solution to the surface or surfaces of said film

21. A method of treating hpmc film comprising:
    a) making a solution of one or more organic acids
    b) applying said solution to the surface or surfaces of said film

22. A method of treating a hpmc film comprising:

    a) making a solution of one or more carboxylic acids
    b) applying said solution to the surface or surfaces of said film

23. A delivery capsule whose walls have adsorbed or absorbed, from the outer side of the walls, a barrier solution comprising one or more carboxylic acids

24. A delivery capsule whose walls have a gradation in concentration of one or more carboxylic acids, through the thickness of the wall

25. A delivery capsule whose walls have a gradation in concentration of one or more carboxylic acids, through the thickness of the wall, wherein the outerpart of the wall possesses the most concentration and the inner part of the wall possesses the most concentration

26. A delivery capsule whose walls have a gradation in concentration of one or more carboxylic acids, through the thickness of the wall, wherein the inner part of the wall possesses the most concentration and the outer part of the wall possesses the least concentration

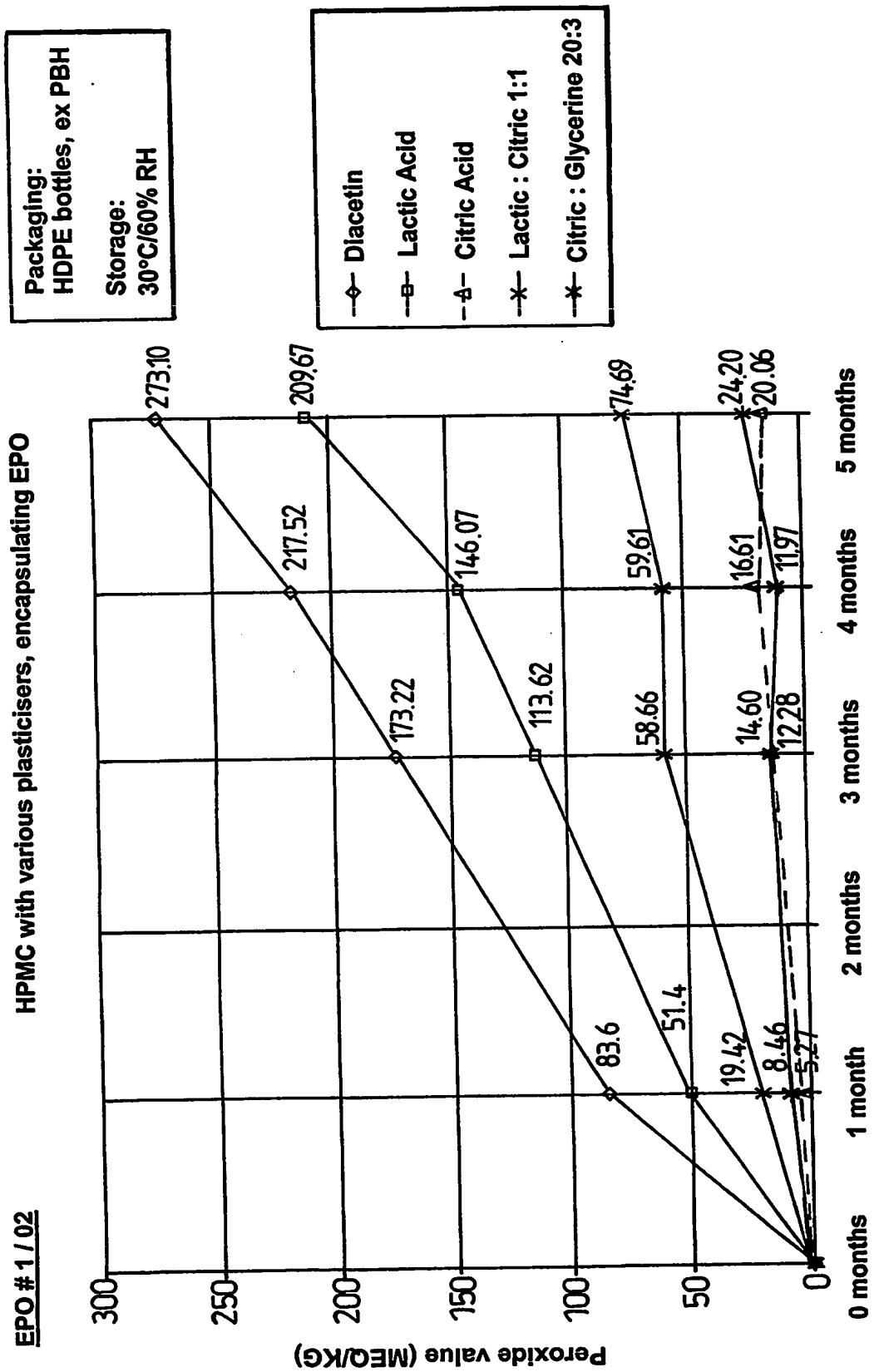
EPO # 1 / 02
HPMC with various plasticisers, encapsulating EPO
Packaging:
HDPE bottles, ex PBH
Storage:
30°C/60% RH
Diacetin
Lactic Acid
Citric Acid
Lactic : Citric 1:1
Citric : Glycerine 20:3
Peroxide value (MEQ/KG)
300
250
200
150
100
50
0
0 months
1 month
2 months
3 months
4 months
5 months
273.10
217.52
173.22
83.6
19.42
8.46
5.27
209.67
146.07
113.62
51.4
74.69
59.61
58.66
24.20
16.61
14.60
20.06
11.97
12.28

Fig. 1

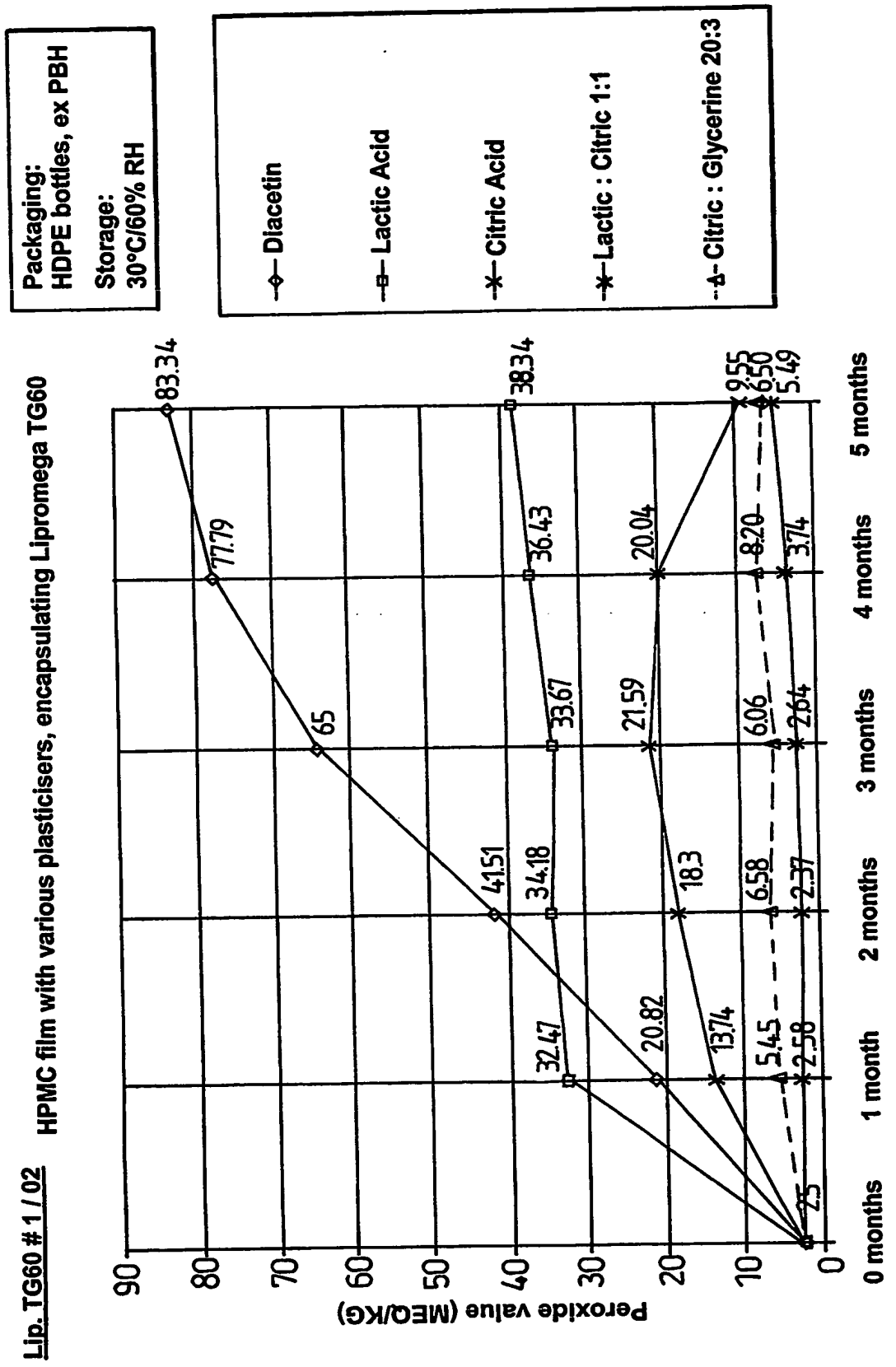
Lip. TG60 # 1 / 02
HPMC film with various plasticisers, encapsulating Lipromega TG60
Packaging:
HDPE bottles, ex PBH
Storage:
30°C/60% RH
Diacetin
Lactic Acid
Citric Acid
Lactic : Citric 1:1
Citric : Glycerine 20:3
Peroxide value (MEQ/KG)
0
10
20
30
40
50
60
70
80
90
0 months
1 month
2 months
3 months
4 months
5 months
83.34
77.79
65
41.51
34.18
32.47
20.82
13.74
5.45
2.58
25
38.34
36.43
33.67
21.59
18.3
6.58
2.37
20.04
8.20
6.06
2.64
9.55
6.50
5.49
3.74

Fig. 2

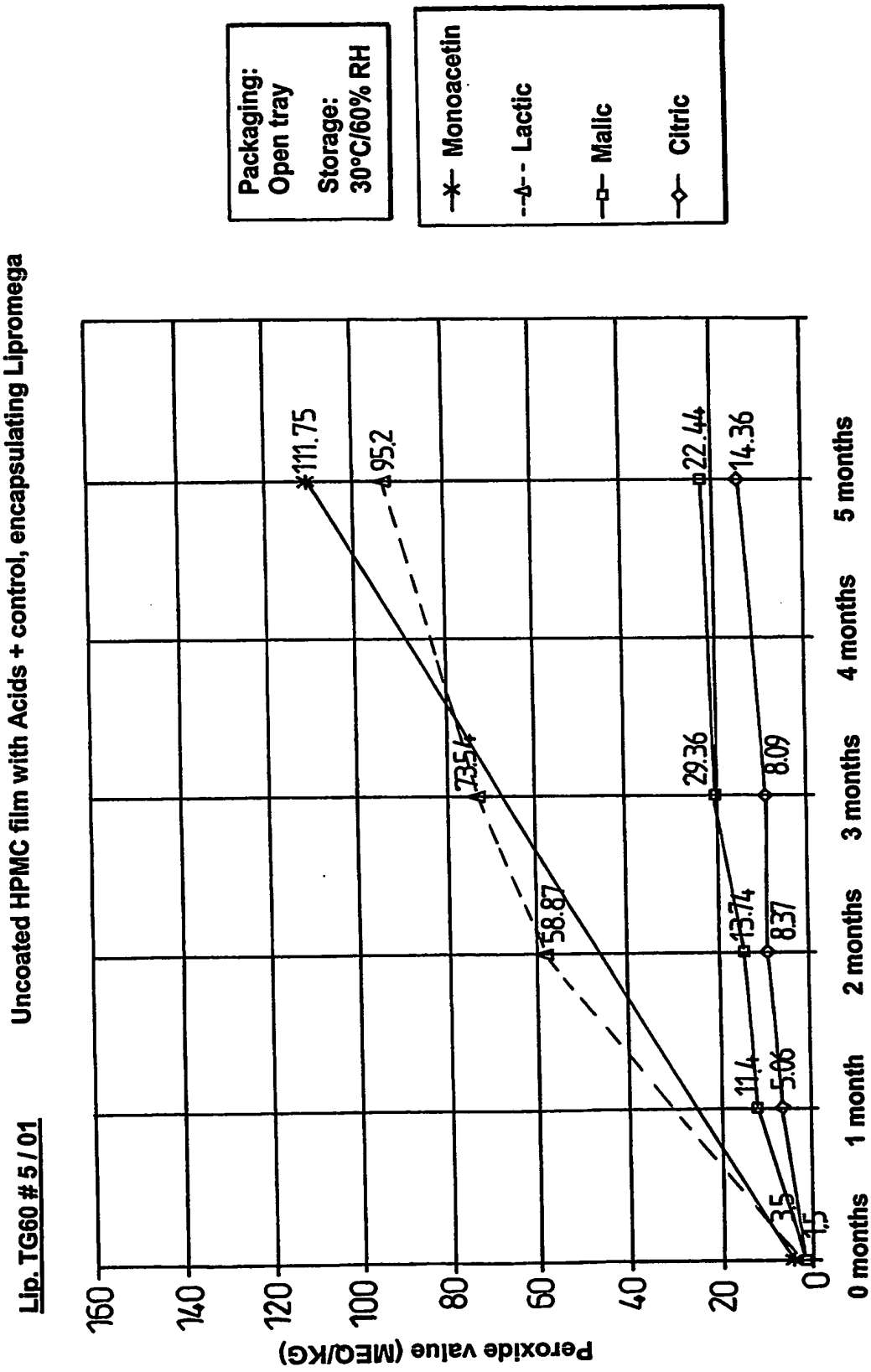
Lip. TG60 # 5 / 01
Uncoated HPMC film with Acids + control, encapsulating Lipromega
Packaging:
Open tray
Storage:
30°C/60% RH
Monoacetin
Lactic
Malic
Citric
Peroxide value (MEQ/KG)
160
140
120
100
80
60
40
20
0
0 months
1 month
2 months
3 months
4 months
5 months
111.75
95.2
73.54
58.87
35
4.5
22.44
14.36
29.36
8.09
13.74
8.37
11.4
5.06

Fig. 3

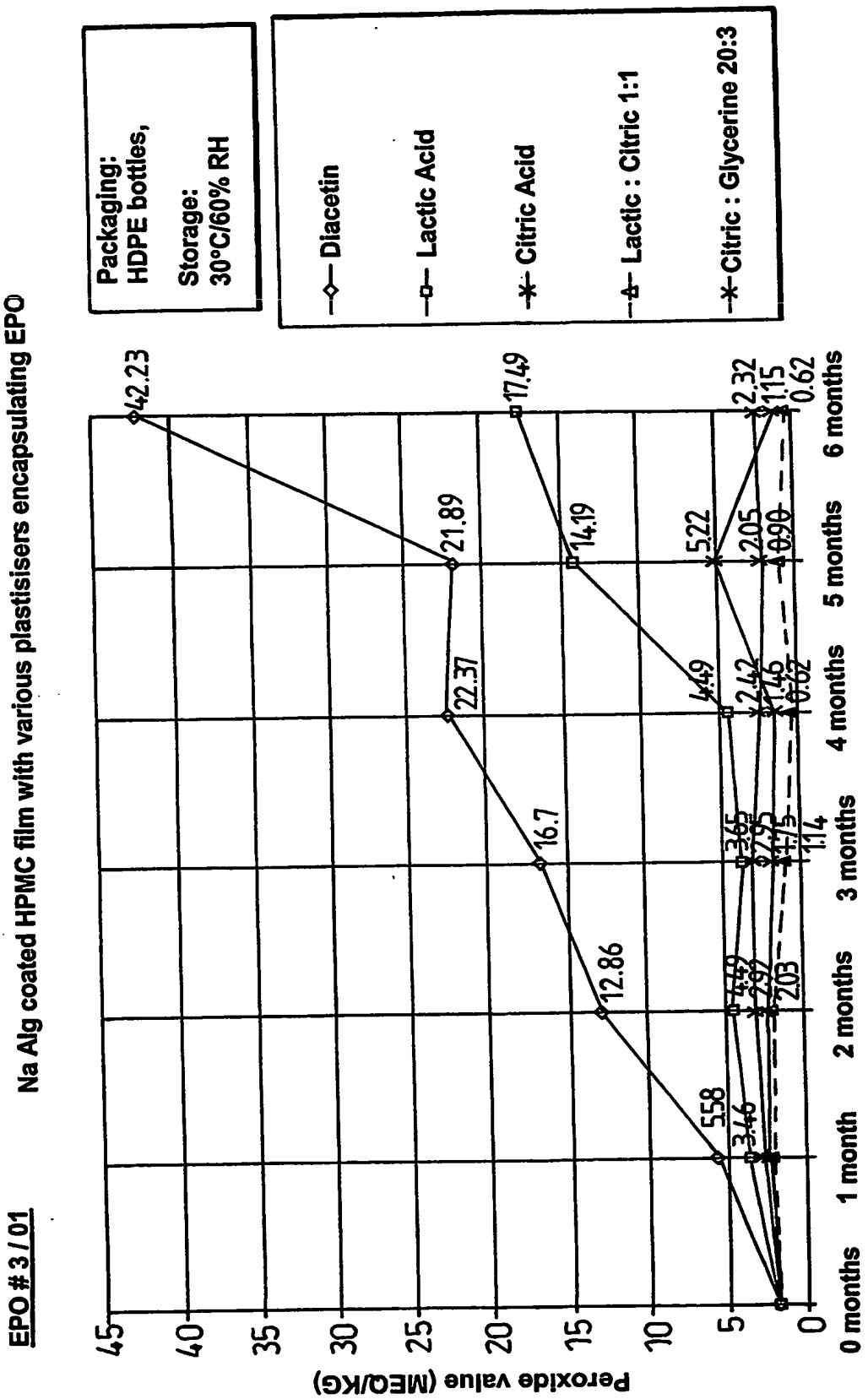
EPO # 3 / 01
Na Alg coated HPMC film with various plastisisers encapsulating EPO
Packaging:
HDPE bottles,
Storage:
30°C/60% RH
Diacetin
Lactic Acid
Citric Acid
Lactic : Citric 1:1
Citric : Glycerine 20:3
Peroxide value (MEQ/KG)
0
5
10
15
20
25
30
35
40
45
0 months
1 month
2 months
3 months
4 months
5 months
6 months
42.23
21.89
22.37
16.7
12.86
5.58
3.46
17.49
14.19
4.49
5.22
2.32
1.15
0.62
2.05
0.90
2.42
1.46
0.62
3.65
1.14
4.49
2.92
2.03

Fig. 4

INTERNATIONAL SEARCH REPORT

PCT/[redacted]3/04083

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/48 C08J5/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C08J C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 095548 A (AYERS VICTORIA JANE ;NOWAK EDWARD ZBYGNIEW (GB); TECKOE JASON (GB)) 20 November 2003 (2003-11-20) page 2 -page 3 ---	1-19
P,X	WO 02 083779 A (AYERS VICTORIA JANE ;NOWAK EDWARD ZBYGNIEW (GB); BIOPROGRESS TECH) 24 October 2002 (2002-10-24) page 2 -page 3 ---	1-19
P,X	WO 02 098394 A (KESSEL STEPHEN RONALD ;NOWAK EDWARD ZBYGNIEW (GB); POVEY IAN DAVID) 12 December 2002 (2002-12-12) page 2 -page 3 page 6, line 1-3 --- -/--	1-15, 17-19, 23-26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2004	30/01/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

PCT/[redacted]03/04083

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 69418 A (DOW CHEMICAL CO) 23 November 2000 (2000-11-23) page 1, line 5-15 page 2, line 10-14 page 3, line 23-26 examples 1,2	1-19
X	DE 32 33 764 A (SCHERER GMBH R P) 15 March 1984 (1984-03-15) examples 1,2 claims 1-3	1-15, 17-19, 23-26
A	WO 02 03968 A (NOWAK EDWARD ZBYGNIEW ;BIOPROGRESS TECH INT INC (GB)) 17 January 2002 (2002-01-17) page 1, paragraph 3 -page 2, paragraph 7	1-26
A	GB 2 343 669 A (BIOPROGRESS TECH INT INC) 17 May 2000 (2000-05-17) page 2	1-26

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INTERNATIONAL SEARCH REPORT

PCT/[redacted]03/04083

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03095548	A	20-11-2003	WO	03095548 A1	20-11-2003
WO 02083779	A	24-10-2002	GB	2374874 A	30-10-2002
			WO	02083779 A1	24-10-2002
			GB	2374343 A	16-10-2002
WO 02098394	A	12-12-2002	WO	02098394 A1	12-12-2002
WO 0069418	A	23-11-2000	AU	4709000 A	05-12-2000
			WO	0069418 A1	23-11-2000
			US	6269157 B1	31-07-2001
DE 3233764	A	15-03-1984	DE	3233764 A1	15-03-1984
WO 0203968	A	17-01-2002	AU	766010 B2	09-10-2003
			AU	5994400 A	30-01-2001
			AU	7431101 A	21-01-2002
			CA	2375616 A1	18-01-2001
			EP	1194130 A1	10-04-2002
			EP	1317255 A1	11-06-2003
			WO	0203968 A1	17-01-2002
			GB	2366780 A	20-03-2002
			JP	2003521287 T	15-07-2003
			US	2003185881 A1	02-10-2003
GB 2343669	A	17-05-2000	AT	248591 T	15-09-2003
			AU	748996 B2	13-06-2002
			AU	3788800 A	29-05-2000
			CA	2348843 A1	18-05-2000
			CZ	20011670 A3	17-10-2001
			DE	69911048 D1	09-10-2003
			EP	1128821 A1	05-09-2001
			WO	0027367 A1	18-05-2000
			JP	2002529398 T	10-09-2002
			US	6352719 B1	05-03-2002